REMARKS

Claims 1-12 are pending in this application. Claims 1-4, 9 and 11 were withdrawn from further consideration as being directed to a non-elected invention. Claims 5 and 6 were rejected under 35 U.S.C. § 112, first paragraph. Claims 5-8, 10 and 12 were variously rejected under 35 U.S.C. § 112, second paragraph. Claims 5, 6, 8, 10 and 12 were rejected under 35 U.S.C. § 103(a).

By this amendment, claims 5-12 have been canceled, and new claims 13 -16 have been added. Claim 1 has been amended without prejudice or disclaimer of any previously claimed subject matter.

Claim 1 is supported by the originally filed claim 1, which is considered part of the original disclosure. As explained herein, it claims the same subject matter covered by original claim 1.

Claims 13 and 14 are supported by the specification at page 4, lines 24-29.

Claim 15 is supported by the specification at page 7, lines 6-19.

Claim 16 is supported by original claim 1, and by the specification at page 4.

The amendments are supported by the originally filed application as indicated above, thus they add no new matter. The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Withdrawal of Claims

Claims 1-4, 9 and 11 were withdrawn from further consideration by the Examiner as being directed to a non-elected invention. The applicants traverse this action, because the Examiner's conclusion is based on a mischaracterization of the original claims.

Claim 1 as originally filed said:

> 1. A method for treating a patient that has osteoporosis and is being administered cyclase activating parathyroid hormone (CAP) or analogues thereof comprising also administering a cyclase inhibiting parathyroid hormone peptide (CIP) having an amino acid sequence from between (SEQ ID No.1 [PTH_{2-84}]) and (SEQ ID No. 2 [PTH_{34-84}]) or a conservatively substituted variant thereof exhibiting parathyroid hormone (PTH) antagonist activity in a therapeutically effective, but non-toxic amount that reduces the occurrence of hypercalcemia or osteosarcoma in the patient resulting from the administration of CAP.

According to the Examiner, this claim was directed to "a method of treating osteoporosis." But what it actually says is "a method for treating a patient": the next phrase, "that has osteoporosis and is being administered...", merely describes which "patient" should be treated. The claimed method "compris[es] also administering a cyclase inhibiting parathyroid hormone peptide (CIP)...in a therapeutically effective, but non-toxic amount that reduces the occurrence of hypercalcemia or osteosarcoma..." This explains that CIP is to be administered in an amount effective to achieve the desired effect of reducing hypercalcemia or osteosarcoma. Respectfully, then, the original claim was directed to a method of using CIP to reduce the side effects—hypercalcemia or osteosarcoma—caused by CAP or an analogue thereof. The original claim was not directed to a method to treat

osteoporosis *per se*, only to a method to reduce the side effects of a CAP treatment given to a patient having osteoporosis.

In the previous action, in response to the Examiner's interpretation of original claim 1, the applicant amended the claims to more clearly point out the intent of the original claims, and presented the following:

> Claim 1. (Amended): A method for reducing the occurrence of hypercalcemia or osteosarcoma in a patient that has received administration of, or is being administered, cyclase activating parathyroid hormone (CAP) or analogues thereof comprising also administering a cyclase inhibiting parathyroid hormone peptide (CIP), which CIP comprises a contiguous portion of PTH having an amino acid sequence set forth in SEQ ID NO:5 (PTH_{1-84}), having an N-terminal amino acid residue starting at any position spanning from position 2 through position 34 of the PTH_{1-84}, and a C-terminal amino acid residue ending at position 84 of the PTH_{1-84}, or a conservatively substituted variant thereof exhibiting parathyroid hormone (PTH) antagonist activity in a therapeutically effective, but non-toxic amount that reduces the occurrence of hypercalcemia or osteosarcoma in the patient resulting from the administration of CAP.

As the Examiner states, the second version of claim 1 does not include a limitation requiring the patient to have osteoporosis, but the applicants believe *it is otherwise an accurate restatement of the original claim*. The Examiner characterized the first version as 'a method to treat osteoporosis' and held that the applicant had constructively elected that invention. The second version was then characterized as a method to reduce hypercalcemia or osteosarcoma, and was withdrawn from consideration by the Examiner because it allegedly claimed a non-elected invention. Then the Examiner concluded that the second version improperly necessitated new grounds of rejection and made the action final.

The applicant asserts that both versions of claim 1 describe the same invention. While perhaps not a model of clarity, if the first version said 'blue hair' instead of 'osteoporosis', i.e., "A

method for treating a patient that has *blue hair* and is being administered cyclase activating parathyroid hormone (CAP)...", the '*blue hair*' would doubtless be recognized as a limitation on the class of patients suitable for the claimed method, and not as a condition being treated. Intellectually, 'osteoporosis' is distracting because it is a treatable condition that is mentioned early in a 'method of treatment' claim. But grammatically, the first version of claim 1 is no less clear than the one with 'blue hair': properly read, the method described in original claim 1 is (1) treating a patient having certain characteristics (2) by administering CIP (3) in an effective amount (4) to reduce osteosarcoma or hypercalcemia; it is *not* describing a method to treat osteoporosis *or* blue hair. The withdrawal of the second version of the claims from consideration based on the allegation that the applicant was prosecuting a new invention was therefore inappropriate, and reconsideration of the decision to withdraw the claims is requested.

Finality of the Office Action.

As explained above, the applicant believes that the Examiner's objections to claims 1-4 as introducing a new invention for prosecution were inappropriate. Therefore, the Examiner's decision to make the rejection final because "applicant's amendment necessitated the new ground(s) of rejection presented" was also improper. The applicant therefore requests that the Examiner also withdraw the finality of the previous office action, and reconsider the second version of the claims in light of the amendments and remarks presented herein.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner also rejected claims 5-8, 10 and 12 as indefinite, because the CAP rebound effect is allegedly not defined or understood in the art. Claim 7 was rejected as incomplete, for allegedly omitting essential steps: the Examiner asserts that it is unclear how to "monitor and guide" the treatment. Furthermore, the claim described a patient having osteoporosis, which lacked antecedent basis. Claims 5-12 have been canceled by the present amendment, obviating these grounds for rejection.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 5 and 6 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably provide enablement for claims to a method for inducing the CAP rebound effect by administering a PTH antagonist to any patient. The Examiner asserts that the "CAP rebound effect" was not sufficiently described in the specification, nor was it clearly understood by one of ordinary skill. Furthermore, these claims were also deemed indefinite because it was unclear what 'patient' would appropriately receive the specified treatment. This, too, is obviated by the present amendment, and the applicant notes that the objection should not apply to the claims now presented, which clearly define the 'patients' for whom the invention is useful.

The applicant appreciates the Examiner's statements summarizing the specification in the interest of compact prosecution. Office Action at pg. 3, last paragraph, and continued on page 4. The Examiner concluded that the claims "are enabled for a method of treating a patient having osteoporosis with the PTH antagonist." The amended claims are drawn to treating such patients, and they are drawn to treatment of such patients to reduce hypercalcemia or osteosarcomas, not to treat osteoporosis *per se*. The amended claims limit the 'patient' to one having osteoporosis who is also receiving or has received treatment comprising CAP or a CAP analogue.

This appears to address the Examiner's objection that the claim as previously written read on *any* patient, and it appears to bring the claims within the scope the Examiner concluded was enabled by the specification. Thus even if the Examiner declines to withdraw the finality of the previous rejection, the applicants request entry of the amended claims since they comply with a recommendation by the Examiner and reduce the issues for appeal.

Rejections under 35 U.S.C. §103(a)

Claims 5, 6, 8, 10 and 12 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Fukuda (U.S. Patent 5,856,138) in view of Kanmera et al., EP 0 451 867. Though these claims have been canceled, the applicant respectfully traverses this rejection to the

extent that the Examiner might have applied it to claims 1-4 had they not been withdrawn by the Examiner.

Fukuda teaches truncated PTH analogs that are alleged to fall within the scope of the CIP of the present claims, and these are taught as useful for treating hypercalcemia and hyperparathyroidism. Kanmera purportedly discloses PTH antagonists useful for treating osteoporosis. From these, the Examiner asserts that it would be obvious to combine the PTH antagonists taught by Fukuda in the treatment of osteoporosis, since Kanmera teaches that PTH antagonists have such utility. The Examiner asserts that osteoporosis treatment achieved by the CAP rebound effect would be inherent in such treatment and thus not patentable, even though not disclosed by either reference.

The applicant has canceled the claims that were thus rejected, and presents no claims drawn to the CAP rebound effect. Nevertheless, as the applicant certainly shares the Examiner's interest in compact prosecution, the applicant recognizes that the obviousness rejections over Kanmera and Fukuda could become applicable to the claims now presented, and offers the following comments.

A *prima facie* case for an obviousness rejection requires the Examiner to demonstrate three things: the cited references must disclose all of the elements of the claimed invention, must provide a motivation to make the combination alleged to be obvious, and must provide one of ordinary skill with a 'reasonable likelihood of success' with that combination. Here, the Examiner relies on Fukuda and Kanmera to assert an obviousness rejection. However, the applicant notes that Fukuda, while disclosing that "compounds in which several amino acid residues on the N-terminal side of PTH (1-34) are deleted are known to function as inhibitors" (Fukuda, col. 2 ll. 27-29) of PTH activity, does not seem to identify any CIP compounds that qualify as PTH 'antagonists'. It says that the invention provides "antagonists in which several amino acid residues on the N-terminal side of human PTH containing the C-terminal peptide are deleted, and peptides obtained by further subjecting the antagonists to the amino acid substitution mentioned above." Such compounds are said to have "more desirable properties in clinical applications." Col. 2, ll. 33-39. But it also says

that "when the resulting human PTH mutein is an agonist derivative, it can be used as therapeutic agents for various diseases caused by the abnormality of calcium metabolism, for example, osteoporosis and hyperparathyroidism", and "the human PTH antagonist derivatives can be used as therapeutic agents for hypercalcemia and hyperparathyroidism." Fukuda, col. 11, lines 18-25. The reference thus lumps together agonists and antagonists rather than identifying which type of compound exhibits what kind of activity. It also discloses that PTH (7-84), which it calls "[Leu8] human PTH" (see Ex. 5, col. 26), has the same biological activity in one assay as intact PTH. Col. 30, table in the Experimental Section. Thus the activity presented indicates that PTH (7-84) acts as an agonist. Thus Fukuda does not provide a clear teaching that CIP is an antagonist or that an antagonist is useful to treat osteoporosis: as the quotation shows, Fukuda teaches that PTH agonists might be useful to treat osteoporosis but pointedly omits using antagonists for osteoporosis. Col. 11, lines 18-25. And since Fukuda fails to teach that CIP is an antagonist, *the combination of Fukuda and Kanmera does not unambiguously disclose using CIP as an antagonist.* Since the combination of references fails to disclose all of the elements of the invention (i.e., there is no teaching that CIP is an antagonist), it cannot provide a *prima facie* case for an obviousness rejection.

The applicant also believes that the use of CIP in a patient being treated with CAP is *inherently* nonobvious. As the Examiner pointed out in a previous office action, "it is highly likely that such a combination would cause no significant net change [or] other biological effect." Office Action dated 14 January 2004, at page 5. CAP and CIP are recognized as an agonist and a corresponding antagonist, which are expected to possess offsetting biological activities. One of ordinary skill familiar with the use of CAP to treat osteoporosis, even in light of Kanmera and / or Fukuda, would not be motivated to use CIP *in combination with CAP* to treat either osteoporosis *or* hypercalcemia. The logical expectation would be, as the Examiner observed, that the combination would cause "no significant net change." The effect of CIP would be expected to offset the effect of CAP, at least in part. Thus the claimed use of CIP in a patient receiving CAP is likewise nonobvious: the ordinary skill and knowledge in the art 'teach away' from such a combination of agonist plus antagonist.

As the specification teaches, however, treatment with CIP in combination with CAP reduces the side effects of CAP treatment without offsetting its beneficial effects. This may seem illogical; *but it is no more illogical than the separate references which teach that both PTH agonists and PTH antagonists can be used to treat osteoporosis.* If the two had *entirely* opposite and offsetting effects in all regards, they could not both separately treat osteoporosis; but they are reported to do so. See Kanmera (Abstract), cited by the Examiner as evidence that a PTH antagonist is useful to treat osteoporosis; and Kretenansky, et al., US 6,051,686, teaching PTH and analogs as treatments for osteporosis, cited by the specification at page 4. Thus their effects are apparently not entirely offsetting, yet one would not be motivated to combine them to treat osteoporosis because the general knowledge in the art indicates they would offset each other just as the Examiner previously asserted.

At best, even with teachings in two references that either CIP or CAP alone can be used to treat osteoporosis, one of ordinary skill might find it 'obvious to try' the combination; but because their activities would generally be understood to offset each other, one would not have a reasonable expectation of success for the combination, only a hope or wish. As the Federal Circuit said in *Jones*, that is not a sufficient basis for a finding of obviousness. See Jones v. Hardy, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1984) ("Obvious to try" is an improper consideration in adjudicating obviousness issue, citing In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977)). Thus the applicants assert that the references cited do not render the claimed invention obvious because the combination does not disclose all elements of the invention; because the skill in the art teaches away from making the combination; and because the knowledge and skill in the art would make one of ordinary skill justifiably dubious that the combination would work.

Finally, the applicant wishes to address the Examiner's rejection in the previous office action, which asserted that the method of treating osteoporosis with a PTH antagonist was not enabled. That objection was directed to claims drawn to a method to treat osteoporosis; as explained above, the present claims clearly are not to treatment of osteoporosis. Still, the Examiner asserted that an effective dose for treating osteoporosis could not be determined without undue experimentation because it takes too long for the effects on osteoporosis to be measurable. The

applicant asserts that the effects on hypercalcemia, for example, could be readily measured and used to guide one of ordinary skill to an appropriate dosage of PTH antagonist in a reasonably short time frame. One of ordinary skill would know to monitor the effectiveness of the CIP treatment by monitoring calcium levels in the treated patient, and methods for doing so are well known. Furthermore, Figure 2 demonstrates that an observable effect on calcium levels occurs almost immediately, showing an effect on hypercalcemia. See also page 7. Thus selecting appropriate methods for delivery and dosages of CIP for a patient could be determined without undue experimentation. *Some* experimentation is routine in the optimization of such treatments for any particular patient, and the Federal Circuit has said that the key word in the phrase requiring enablement "without undue experimentation" is "undue"; the fact that some experimentation is necessary does not render the specification deficient. *In re Wands*, 858 F.2d at 736-37, 8 U.S.P.Q.2D (BNA) at 1404 (Fed. Cir. 1988) ("The key word is 'undue,' not 'experimentation.'") Thus the applicant asserts that the claimed invention is enabled by the specification as it would be understood by one of ordinary skill in the art.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw all outstanding rejections of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 532212000200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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